

The pathway to precision pest control:

Species-specific toxin development

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Manaaki Whenua
Landcare Research



The pathway to precision pest control:

Species-specific toxin development



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1. Why?

2. Research approach

3. Progress and path forward

Introduced mammals are devastating for NZ's native wildlife



An expanded toxin toolbox would help to achieve our pest control goals in Aotearoa



New toxin wishlist for pest control

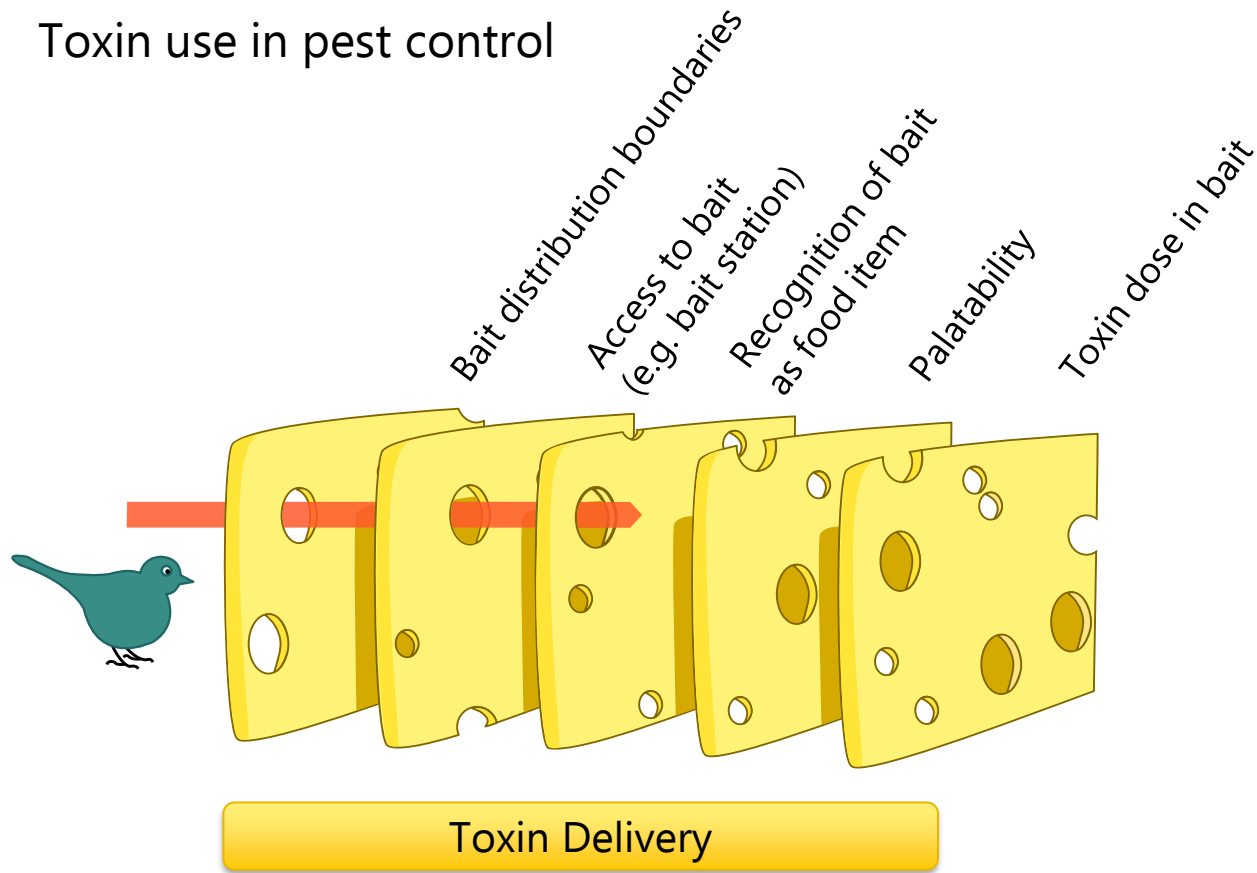


- Highly selective
 - Species-specific or family-specific
- Improved animal welfare
- Low environmental impact
- Cost effective
- Easy to manufacture
- e.t.c...



Swiss Cheese Model of Risk Management

Toxin use in pest control



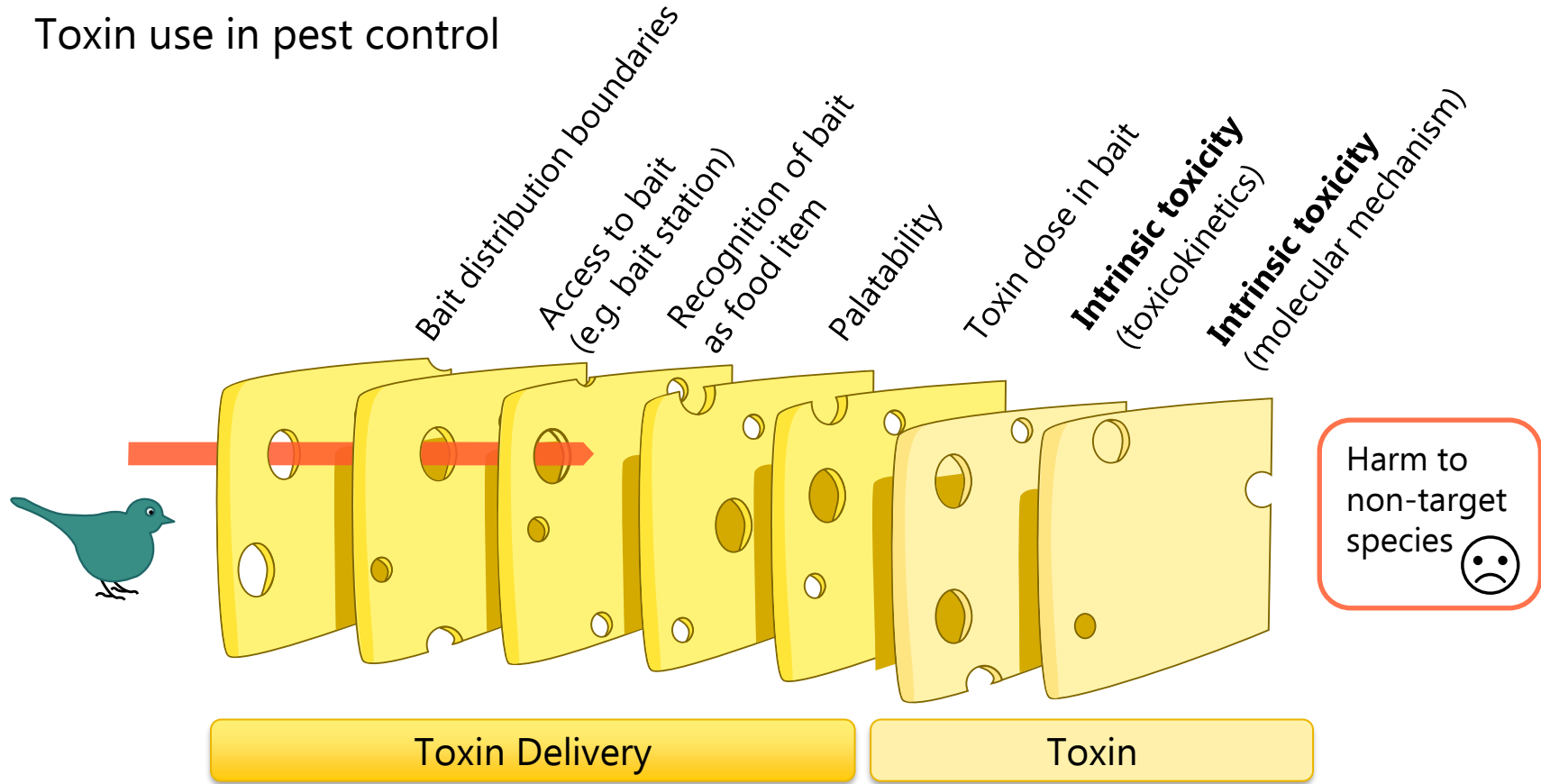
Harm to non-target species





Swiss Cheese Model of Risk Management

Toxin use in pest control



The pathway to precision pest control:

Species-specific toxin development



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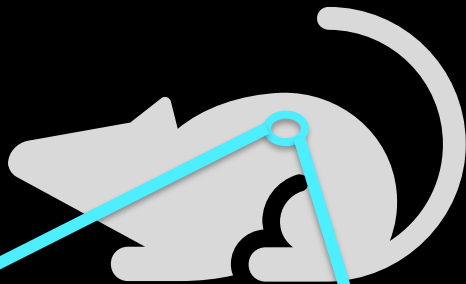


1. Why?

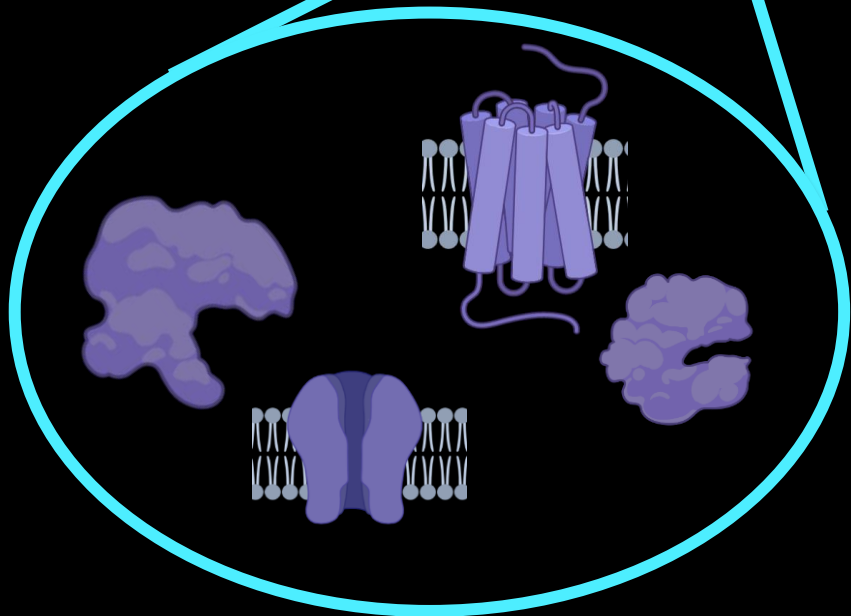
2. Research approach

3. Progress and path forward

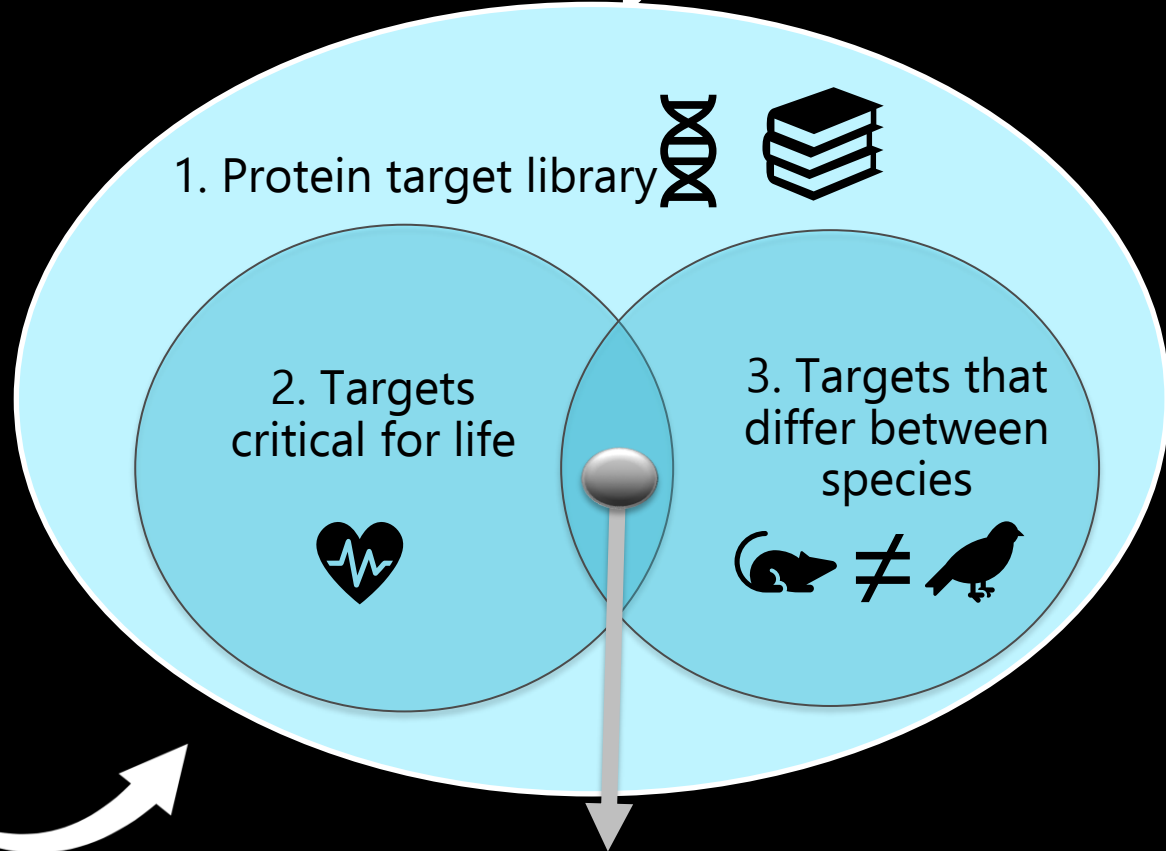
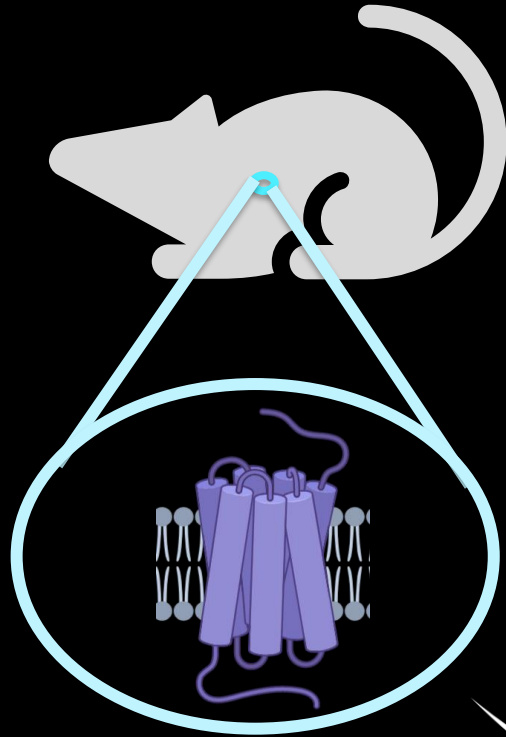
Toxin
/Drug



Toxicity 
/Biological response



Target-driven toxin discovery

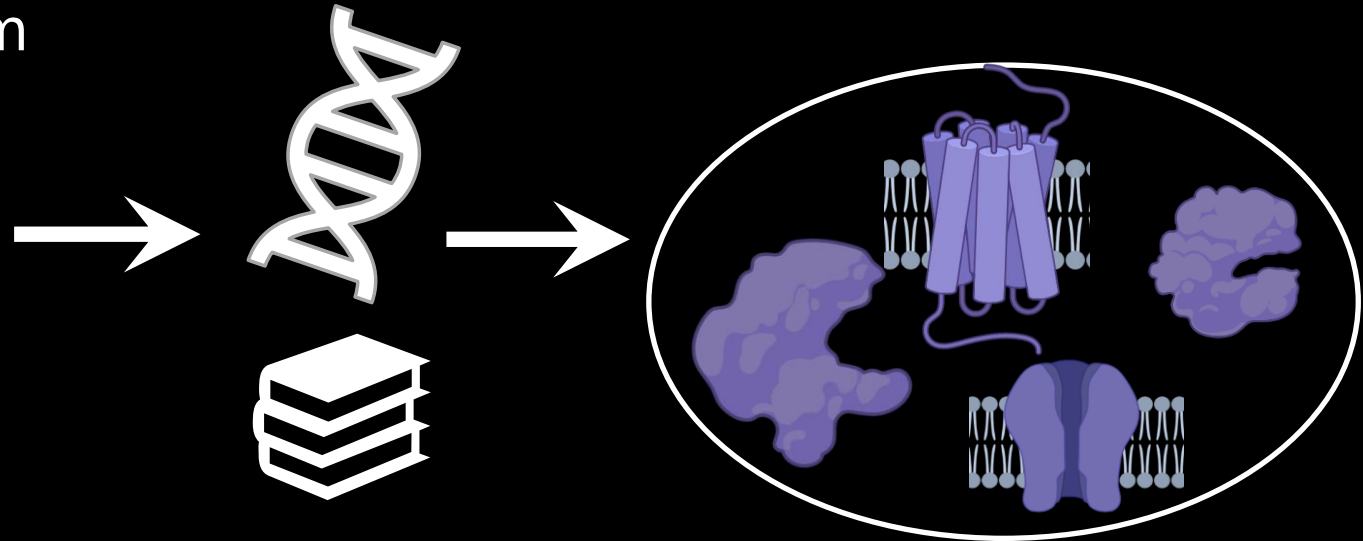


Potential toxin targets for validation



1. Genomes provide protein target library

- Recent development
- Genomes now available for:
 - Stoat
 - Ship rat
 - Possum

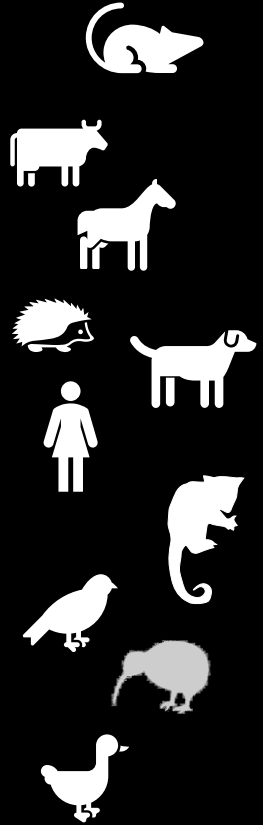
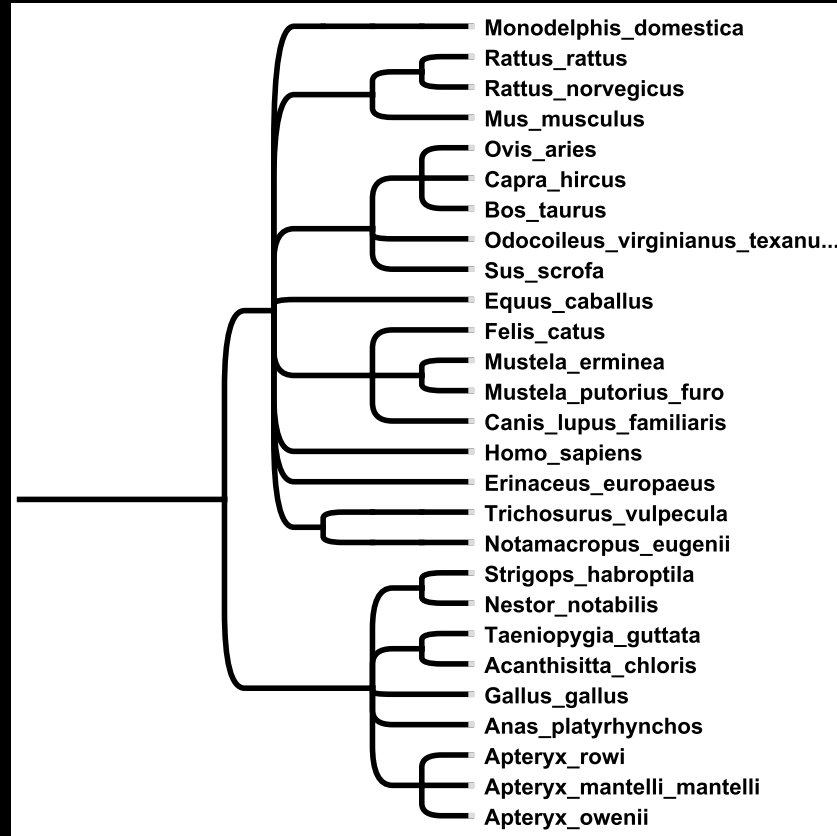




1. Genomes provide protein target library



- Target pests
- Non-target species
 - Birds,
 - Livestock
 - Humans

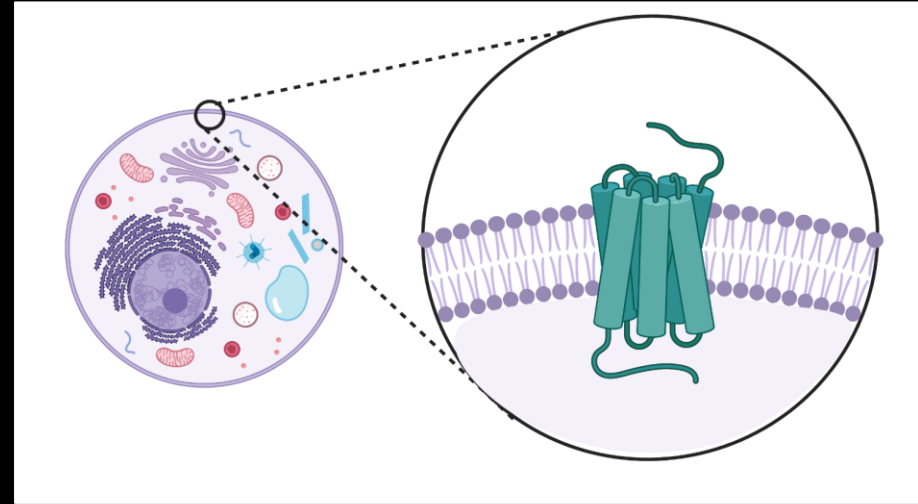




2. Identify proteins critical for life



- G protein-coupled receptors
 - Transmembrane proteins
 - Physiologically important
 - Highly druggable
- Well-studied
- Chemical probes available

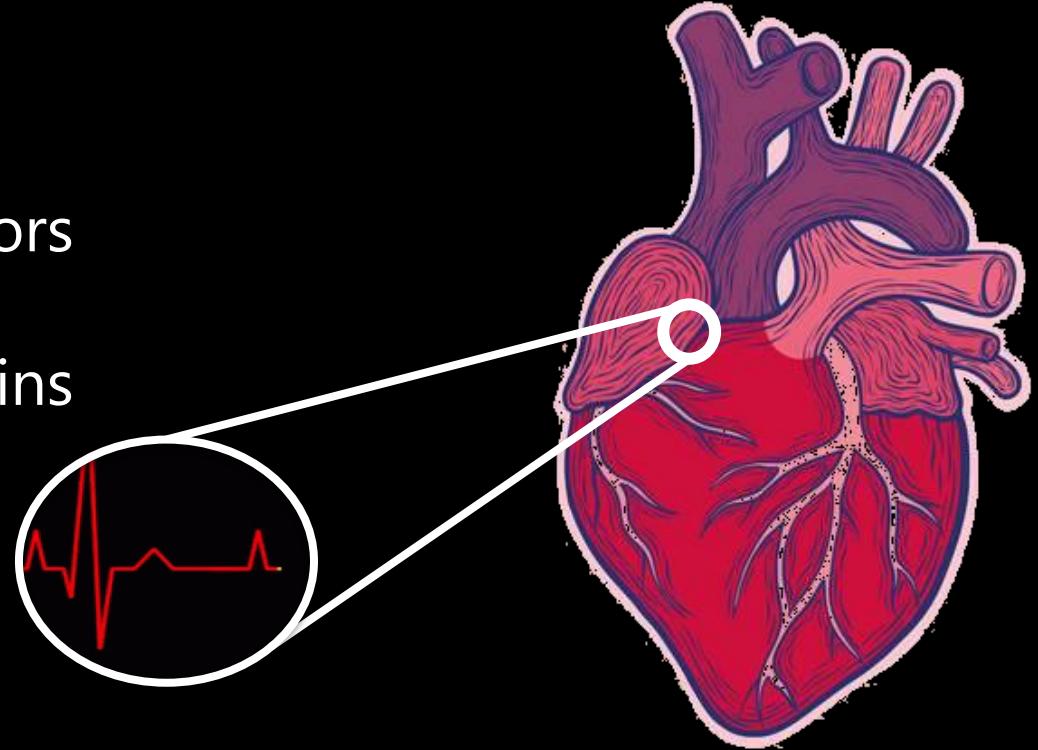


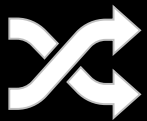


2. Identify proteins critical for life



- Identify groups of genes critical for life
- G protein-coupled receptors
 - Highly druggable
 - Transmembrane proteins
- Cardiac function genes

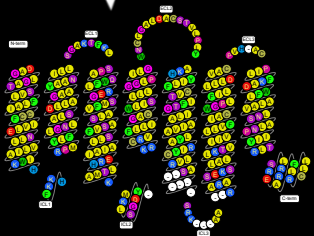
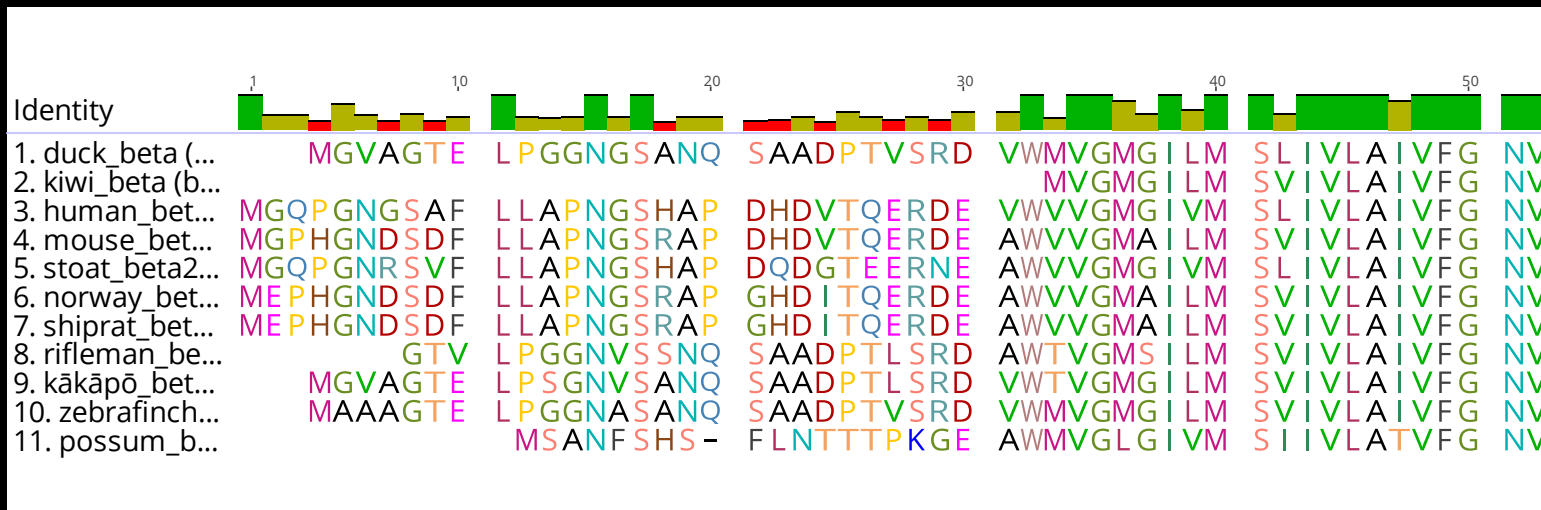


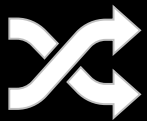


3. Identify targets that differ between species



- Use sequence alignment to identify differences across species

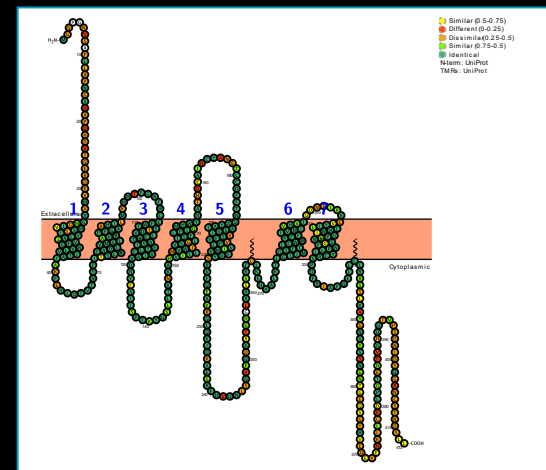
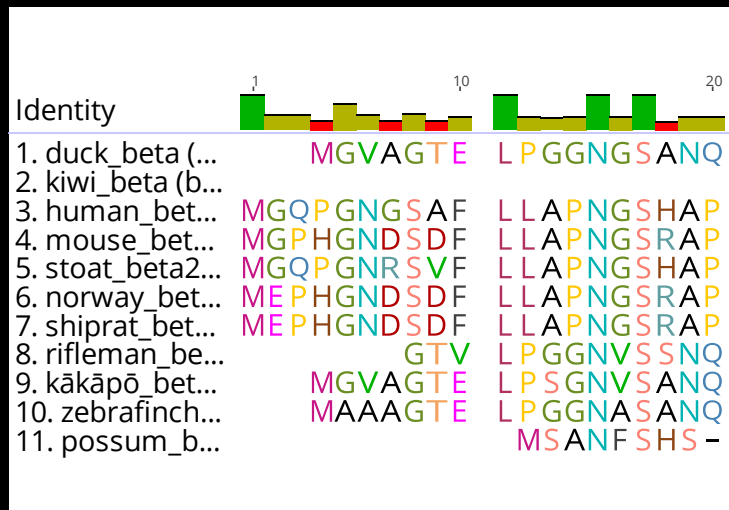
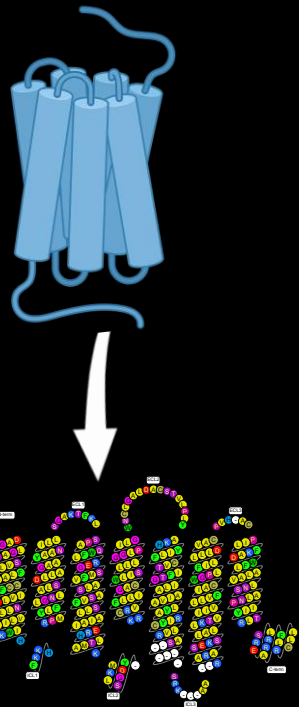


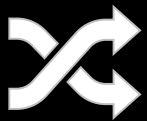


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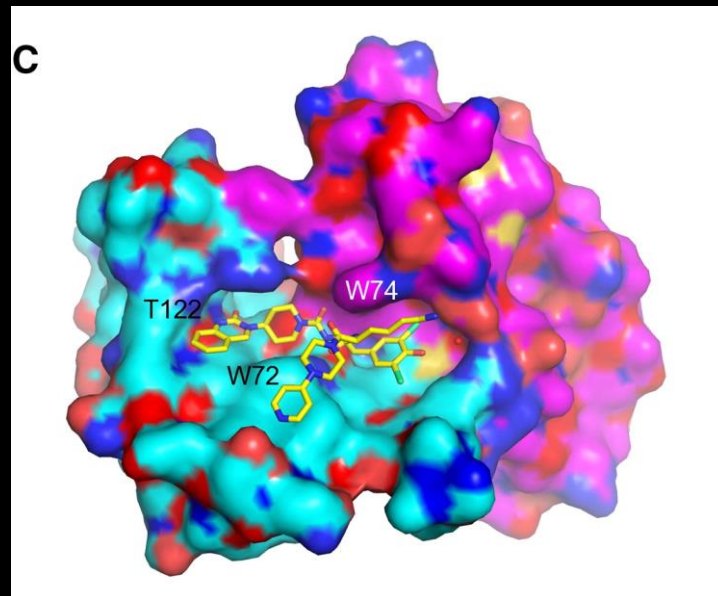


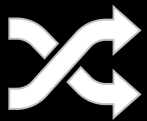


3. Identify targets that differ between species



- How different do target proteins need to be between species?
- Exact sequence identity will depend on location – functional domain
- Examples of species-specific pharmacology based on as little as 1 amino acid



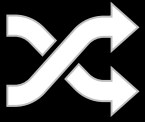


3. Identify targets that differ between species



- Defining 'species-specificity'

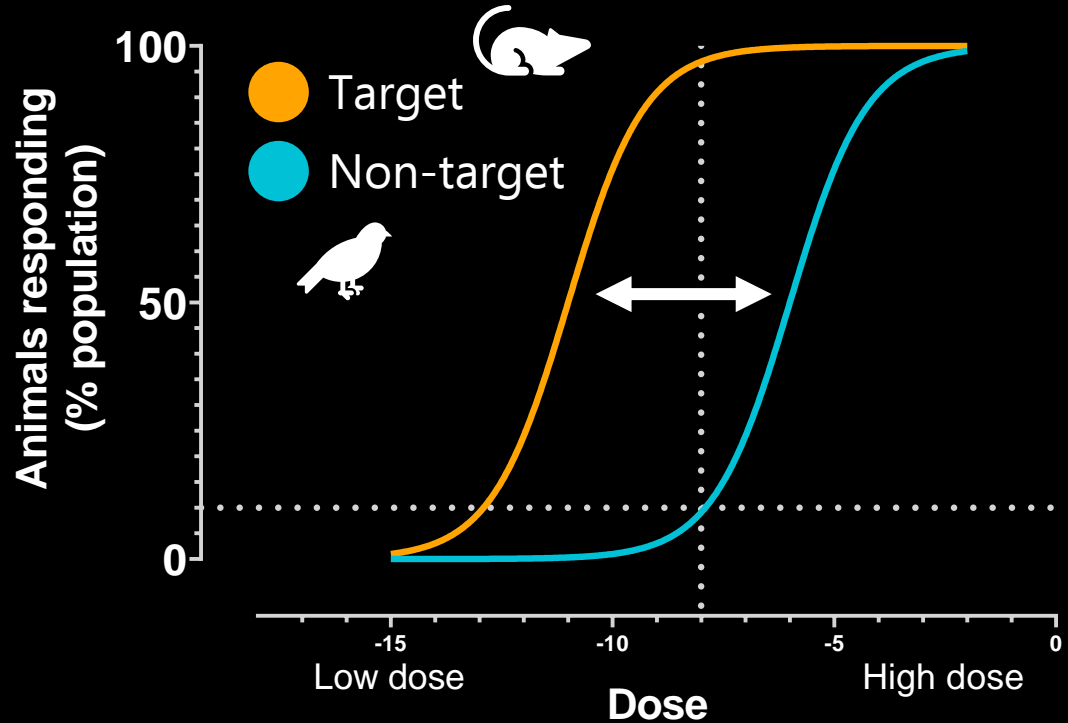




3. Identify targets that differ between species



- Defining 'species-specificity'
- Toxin should be able to distinguish between animals



Computational Pipeline



= genome
mining

GPCRs

- BLASTP and TBLASTN for initial screen
- Guide to Pharmacology list of GPCRs = bait seq

Domains

- Confirm 7 transmembrane domains (Pfam, HMMER)
- Custom Python script

Orthologs

- OrthoFinder, reciprocal BLAST, annotation
- Custom R script

Sequence
identity

- MUSCLE, MAFFT, Clustal
- Protein models using PyMol and MODELLER



What is NeSI?

New Zealand eScience Infrastructure

(NeSI) designs, builds, and operates a specialised platform of shared high performance computing infrastructure and a range of eResearch services.

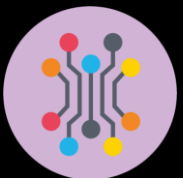
All researchers in New Zealand have access to NeSI.

Contact support@nesi.org.nz

NeSI is a national collaboration of:



NeSI
New Zealand eScience
Infrastructure



High performance computing (HPC) and analytics



Data services

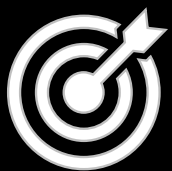


Training and researcher skill development

- Training to grow capabilities in NZ research sector
- Partnership with The Carpentries and Genomics Aotearoa for bioinformatics training



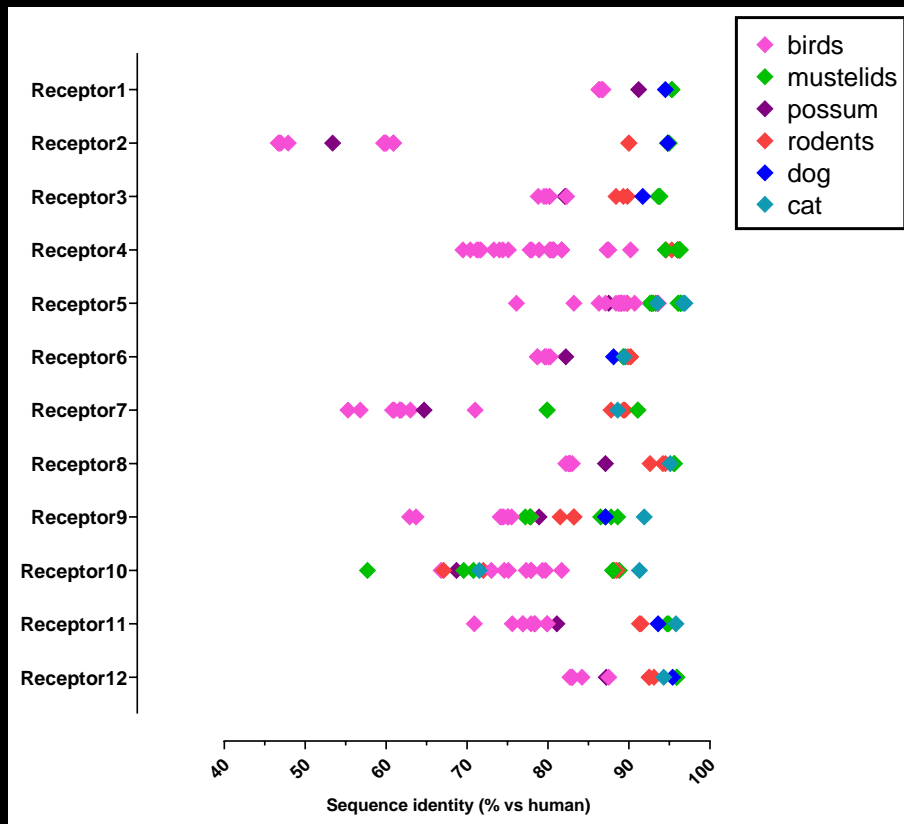
Consultancy



Results



1. Predictable
2. Variation
3. Outliers





Target validation

Disease
association

Expression
profile

Genetic
variants

Molecular
pharmacology

Transgenics

Protein structure
and dynamics

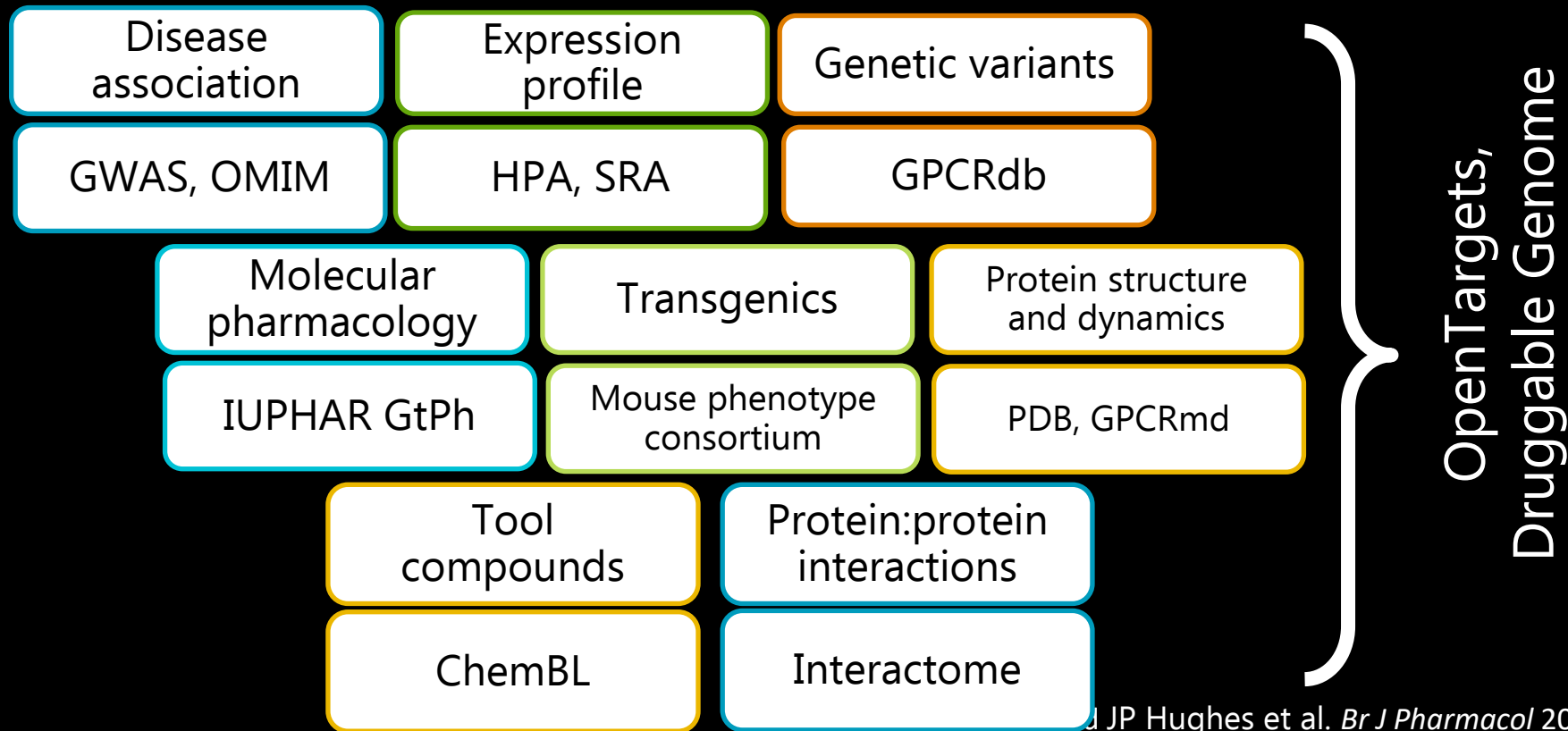
Tool
compounds

Protein:protein
interactions

OpenTargets,
Druggable Genome



Target validation

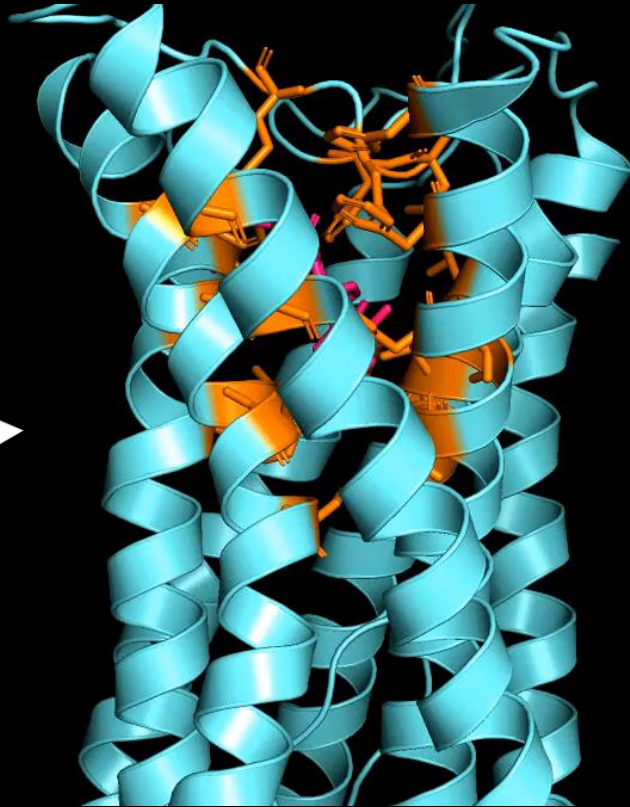
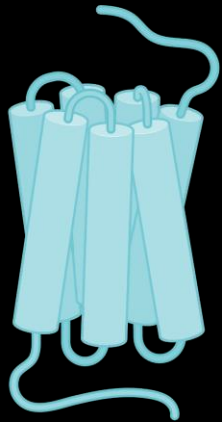




Validate target



- 3D protein homology modelling
- Stoaat receptor





Thanks!

Any questions?



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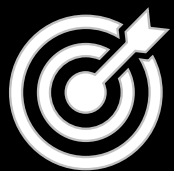
Acknowledgements:

Brian Hopkins
Andrew Veale

Wildlife Ecology and Management team
Genomics Aotearoa
NeSI, Aleksandra Pawlik

“It's crazy and ambitious, but I think it might be worth a shot”

Sir Paul Callaghan



Validate target

Targets

